Response Under 37 C.F.R. §1.192
Appellant's Brief

Application No. 10/057,339
Paper Dated: June 14, 2005
Attorney Docket No. CV01490K

06-15-05

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1617

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Patent Application of Teddy Kosoglou et al.	Examiner: Russell S. Travers
Application No.: 10/057,339	Group Art Unit: 1617
Filed: January 25, 2002	Atty. Docket No.: CV01490K
For: Combinations of Sterol Absorption Inhibitor(s) with Cardiovascular Agent(s) for the Treatment of Vascular Conditions	

MAIL STOP APPEAL BRIEF – PATENTS
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ON APPEAL FROM THE PRIMARY EXAMINER TO THE BOARD OF PATENT APPEALS AND INTERFERENCES

APPELLANT'S BRIEF UNDER 37 C.F.R. § 1.192

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Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Total Number of Pages in This Submission	88

Application Number	10/057,339
Filing Date	January 25, 2002
First Named Inventor	Teddy Kosoglou
Art Unit	1617
Examiner Name	Russell S. Travers
Attorney Docket Number	CV01490K – 4686-050450

ENCLOSURES *(check all that apply)*

- [X] Fee Transmittal Form
  - [X] Fee Attached
- [ ] Amendment / Reply
  - [ ] After Final
  - [ ] Affidavits/declaration(s)
- [ ] Extension of Time Request
- [ ] Express Abandonment Request
- [ ] Information Disclosure Statement
- [ ] Certified Copy of Priority Document(s)
- [ ] Response to Missing Parts/ Incomplete Application
  - [ ] Response to Missing Parts Under 37 CFR 1.52 or 1.53
- [ ] Drawing(s)
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- [ ] Petition
- [ ] Petition to convert to a Provisional Application
- [ ] Power of Attorney, Revocation Change of Correspondence Address
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- [ ] After Allowance communication to TC
- [X] Appeal Communication to Board of Appeals and Interferences
- [ ] Appeal Communication to TC **(Appeal Notice, Brief, Reply Brief)**
- [ ] Proprietary Information
- [ ] Status Letter
- [ ] Other Enclosure(s) (please identify below):

Remarks

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm Name	The Webb Law Firm		
Signature	Debra Z. Anderson		
Printed Name	Debra Z. Anderson		
Date	June 14, 2005	Reg. No.	44,506

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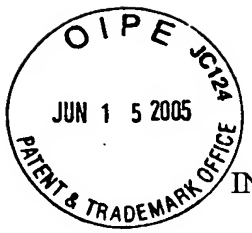

PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF:	ATTORNEY'S DOCKET NUMBER
Teddy Kosoglou et al.	**CV01490K (4686-050450)**

ENTITLED

"Combinations of Sterol Absorption Inhibitor(s) with Cardiovascular Agent(s) for the Treatment of Vascular Conditions"

Mail Stop Appeal Brief - Patents
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Effective on 12/08/2004.
Fees pursuant to the Consolidated Appropriations Act, 2005 (H.R. 4818)

FEE TRANSMITTAL For FY 2005

☐ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT	($) 500.00

Complete if Known	
Application Number	10/057,339
Filing Date	January 25, 2002
First Named Inventor	Teddy Kosoglou
Examiner Name	Russell S. Travers
Art Unit	1617
Attorney Docket No.	CV01490KUS – 4686-050450

METHOD OF PAYMENT (check all that apply)

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FEE CALCULATION

1. BASIC FILING, SEARCH, AND EXAMINATION FEES

	FILING FEES		SEARCH FEES		EXAMINATION FEES		
		Small Entity		Small Entity		Small Entity	
Application Type	**Fee ($)**	**Fee ($)**	**Fee ($)**	**Fee ($)**	**Fee ($)**	**Fee ($)**	**Fees Paid ($)**
Utility	300	150	500	250	200	100	
Design	200	100	100	50	130	65	
Plant	200	100	300	150	160	80	
Reissue	300	150	500	250	600	300	
Provisional	200	100	0	0	0	0	

2. EXCESS CLAIM FEES

Fee Description	Fee ($)	Small Entity Fee ($)
Each claim over 20 or, for Reissues, each claim over 20 and more than in the original patent	50	25
Each independent claim over 3 or, for Reissues, each independent claim more than in the original patent	200	100
Multiple dependent claims	360	180

Total Claims		**Extra Claims**	**Fee ($)**		**Fee Paid ($)**
_____	- 20 or HP =	_____	x _____	=	_____

HP = highest number of total claims paid for, if greater than 20

Indep. Claims		**Extra Claims**	**Fee ($)**		**Fee Paid ($)**
_____	- 3 or HP =	_____	x _____	=	_____

HP = highest number of independent claims paid for, if greater than 3

Multiple Dependent Claims	
Fee ($)	**Fee Paid ($)**
_____	_____

3. APPLICATION SIZE FEE

If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).

Total Sheets		**Extra Sheets**		**Number of each additional 50 or fraction thereof**		**Fee ($)**		**Fee Paid ($)**
_____	- 100 =	_____	/ 50 =	_____	(round **up** to a whole number)	x _____	=	_____

4. OTHER FEE(S)

	Fee Paid ($)
Non-English Specification, $130 fee (no small entity discount)	_____
Other: Filing a brief in support of an Appeal	500.00

SUBMITTED BY

Signature	Debra Z. Anderson	Registration No. (Attorney/Agent) 44,506	Telephone 412-471-8815
Name (Print/Type)			Date June 14, 2005

TABLE OF CONTENTS

I

REAL PARTY IN INTEREST

The real party in interest in this Appeal is assignee Schering Corporation, having a principal place of business 2000 Galloping Hill Road, Kenilworth, NJ 07033.

II

RELATED APPEALS AND INTERFERENCES

As the legal representative of Appellant, the undersigned attorney has no knowledge of any appeals or interferences directly related to this Appeal.

III

STATUS OF CLAIMS

Claims 1, 3, 22, 23, 33, 34, 43-46 and 49 of this patent application are pending. Claims 4-10, 12-21, 24-32, 35-42, 47 and 48 have been withdrawn by the Examiner as being drawn to a non-elected invention. Claims 2 and 11 were cancelled and the subject matter incorporated into Claims 1 and 49.

Claims 1, 3, 22, 23, 33, 34, 43-46 and 49 were finally rejected under 35 U.S.C. §103(a) in an Office Action mailed January 27, 2005 ("Final Office Action") and an Advisory Action mailed April 11, 2005 ("Advisory Action").

Eleven (11) pending claims (Claims 1, 3, 22, 23, 33, 34, 43-46 and 49) are at issue in this Appeal.

IV

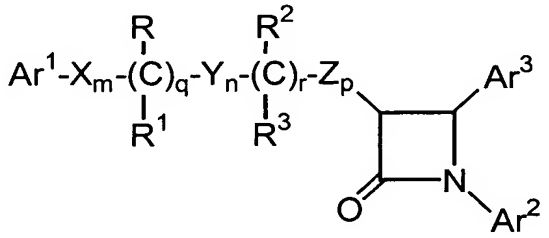
STATUS OF AMENDMENTS

No claims were amended after final rejection. A copy of the claims involved in this Appeal is contained in the Appendix attached hereto.

V

SUMMARY OF CLAIMED SUBJECT MATTER

In one embodiment set forth in claim 1, Applicants have discovered a composition comprising (a) at least one sterol absorption inhibitor represented by Formula (I):



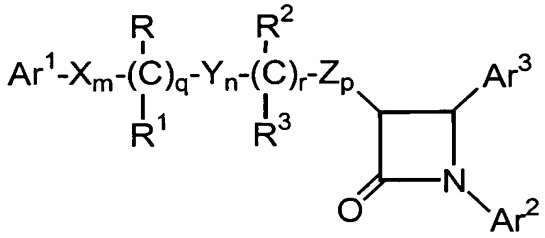
(I)

or isomers thereof, or pharmaceutically acceptable salts or solvates of the compounds of Formula (I) or of the isomers thereof, wherein Ar^1 and Ar^2 are independently selected from the group consisting of aryl and R^4-substituted aryl; Ar^3 is aryl or R^5-substituted aryl; X, Y and Z are independently selected from the group consisting of $-CH_2-$, -CH(lower alkyl)- and -C(dilower alkyl)-; R and R^2 are independently selected from the group consisting of $-OR^6$, $-O(CO)R^6$, $-O(CO)OR^9$ and $-O(CO)NR^6R^7$; R^1 and R^3 are independently selected from the group consisting of hydrogen, lower alkyl and aryl; q is 0 or 1; r is 0 or 1; m, n and p are independently selected from 0, 1, 2, 3 or 4; provided that at least one of q and r is 1, and the sum of m, n, p, q and r is 1, 2, 3, 4, 5 or 6; and provided that when p is 0 and r is 1, the sum of m, q and n is 1, 2, 3, 4 or 5; R^4 is 1-5 substituents independently selected from the group consisting of lower alkyl, $-OR^6$, $-O(CO)R^6$, $-O(CO)OR^9$, $-O(CH_2)_{1-5}OR^6$, $-O(CO)NR^6R^7$, $-NR^6R^7$, $-NR^6(CO)R^7$, $-NR^6(CO)OR^9$, $-NR^6(CO)NR^7R^8$, $-NR^6SO_2R^9$, $-COOR^6$, $-CONR^6R^7$, $-COR^6$, $-SO_2NR^6R^7$, $S(O)_{0-2}R^9$, $-O(CH_2)_{1-10}-COOR^6$, $-O(CH_2)_{1-10}CONR^6R^7$, -(lower alkylene)$COOR^6$, $-CH=CH-COOR^6$, $-CF_3$, -CN, $-NO_2$ and halogen; R^5 is 1-5 substituents independently selected from the group consisting of $-OR^6$, $-O(CO)R^6$,

$-O(CO)OR^9$, $-O(CH_2)_{1-5}OR^6$, $-O(CO)NR^6R^7$, $-NR^6R^7$, $-NR^6(CO)R^7$, $-NR^6(CO)OR^9$, $-NR^6(CO)NR^7R^8$, $-NR^6SO_2R^9$, $-COOR^6$, $-CONR^6R^7$, $-COR^6$, $-SO_2NR^6R^7$, $S(O)_{0-2}R^9$, $-O(CH_2)_{1-10}-COOR^6$, $-O(CH_2)_{1-10}CONR^6R^7$, -(lower alkylene)$COOR^6$ and $-CH=CH-COOR^6$; R^6, R^7 and R^8 are independently selected from the group consisting of hydrogen, lower alkyl, aryl and aryl-substituted lower alkyl; and R^9 is lower alkyl, aryl or aryl-substituted lower alkyl; and (b) at least one cardiovascular agent for treating vascular conditions selected from the group consisting of channel blockers, adrenergic blockers, adrenergic stimulants, angiotensin-converting enzyme (ACE) inhibitors, antihypertensive agents, angiotensin II receptor antagonists, anti-anginal agents, coronary vasodilators, diuretics and combinations thereof. See original claims 1, 2 and 11; page 5, lines 8-20 of the specification and page 19, line 1 to page 20, line 13 of the specification.

In another embodiment set forth in Claim 49, Applicants have discovered a therapeutic combination comprising:

(a) a first amount of at least one sterol absorption inhibitor represented by Formula (I):



(I)

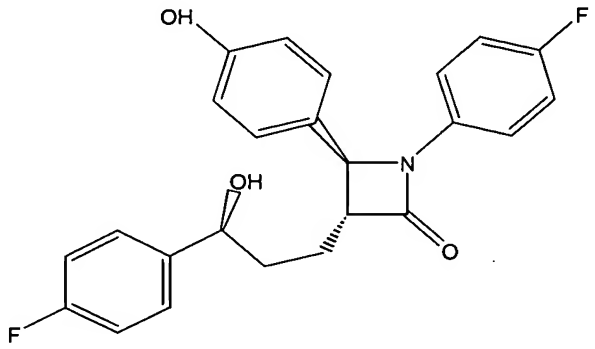
or isomers thereof, or pharmaceutically acceptable salts or solvates of the compounds of Formula (I) or of the isomers thereof, wherein: Ar^1 and Ar^2 are independently selected from the group consisting of aryl and R^4-substituted aryl; Ar^3 is aryl or R^5-substituted aryl; X, Y and Z are independently selected from the group consisting of $-CH_2-$, -CH(lower alkyl)- and -C(dilower alkyl)-; R and R^2 are independently selected from the group consisting of $-OR^6$, $-O(CO)R^6$, $-O(CO)OR^9$ and $-O(CO)NR^6R^7$; R^1 and R^3 are independently

selected from the group consisting of hydrogen, lower alkyl and aryl; q is 0 or 1; r is 0 or 1; m, n and p are independently selected from 0, 1, 2, 3 or 4; provided that at least one of q and r is 1, and the sum of m, n, p, q and r is 1, 2, 3, 4, 5 or 6; and provided that when p is 0 and r is 1, the sum of m, q and n is 1, 2, 3, 4 or 5; R^4 is 1-5 substituents independently selected from the group consisting of lower alkyl, $-OR^6$, $-O(CO)R^6$, $-O(CO)OR^9$, $-O(CH_2)_{1-5}OR^6$, $-O(CO)NR^6R^7$, $-NR^6R^7$, $-NR^6(CO)R^7$, $-NR^6(CO)OR^9$, $-NR^6(CO)NR^7R^8$, $-NR^6SO_2R^9$, $-COOR^6$, $-CONR^6R^7$, $-COR^6$, $-SO_2NR^6R^7$, $S(O)_{0-2}R^9$, $-O(CH_2)_{1-10}$-$COOR^6$, $-O(CH_2)_{1-10}CONR^6R^7$, -(lower alkylene)$COOR^6$, -CH=CH-$COOR^6$, $-CF_3$, -CN, $-NO_2$ and halogen; R^5 is 1-5 substituents independently selected from the group consisting of $-OR^6$, $-O(CO)R^6$, $-O(CO)OR^9$, $-O(CH_2)_{1-5}OR^6$, $-O(CO)NR^6R^7$, $-NR^6R^7$, $-NR^6(CO)R^7$, $-NR^6(CO)OR^9$, $-NR^6(CO)NR^7R^8$, $-NR^6SO_2R^9$, $-COOR^6$, $-CONR^6R^7$, $-COR^6$, $-SO_2NR^6R^7$, $S(O)_{0-2}R^9$, $-O(CH_2)_{1-10}$-$COOR^6$, $-O(CH_2)_{1-10}CONR^6R^7$, -(lower alkylene)$COOR^6$ and -CH=CH-$COOR^6$; R^6, R^7 and R^8 are independently selected from the group consisting of hydrogen, lower alkyl, aryl and aryl-substituted lower alkyl; and R^9 is lower alkyl, aryl or aryl-substituted lower alkyl; and (b) a second amount of at least one cardiovascular agent selected from the group consisting of channel blockers, adrenergic blockers, adrenergic stimulants, angiotensin-converting enzyme (ACE) inhibitors, antihypertensive agents, angiotensin II receptor antagonists, anti-anginal agents, coronary vasodilators, diuretics and combinations thereof, wherein the first amount and the second amount together comprise a therapeutically effective amount for the treatment or prevention of a vascular condition, obesity, diabetes or lowering a concentration of a sterol in plasma of a mammal. See original Claim 49 and page 4, line 31 to page 5, line 7 of the specification.

In the Office Action of March 19, 2004, Applicants were required to elect a composition or method of treating or preventing vascular disorders with active agents as defined by various formulae, including Formula II.

Applicants provisionally elected with traverse Group V, compounds of Formula II, as the active agent, wherein the cardiovascular agent is an antihypertensive agent. See Response to Restriction Requirement and Election of Species of April 19, 2004 ("Response") at pages 1 and 2.

Applicants provisionally elected with traverse ezetimibe as the specific sterol absorption inhibitor, represented by Formula (II) below:



(II).

Ezetimibe is the active ingredient in ZETIA™ (ezetimibe) pharmaceutical formulation and VYTORIN™ (ezetimibe/simvastatin) pharmaceutical formulation, both of which are commercially available from MSP (Merck Schering-Plough) Pharmaceuticals, Inc. See Response to Restriction Requirement and Election of Species of April 19, 2004 ("Response") at page 2.

The claimed compositions and combinations can be useful for treating or preventing atherosclerosis, other vascular diseases and conditions associated with vascular diseases such as hypertension, atherosclerosis, and hyperlipidaemia (page 3, lines 19-22 of the specification), stroke, obesity and lowering of plasma levels of cholesterol in a subject (page 75, lines 13-18 of the specification).

VI

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

I. Has a Prima Facie Case of Obviousness Under 35 U.S.C. § 103 Over Rosenblum et al. in view of Chobanian et al. Been Established?

II. Has a Prima Facie Case of Obviousness Under 35 U.S.C. § 103 Over Rosenblum et al. and Chobanian et al., and further in view of Lelek et al., Myasnikov and Schaarmann et al. Been Established?

VII

ARGUMENT

I. The Required Prima Facie Case of Obviousness Under 35 U.S.C. § 103 Over Rosenblum et al. in view of "Chobanian et al." Has Failed to be Established

A. The Rejection

Claims 1, 3, 22-23, 33-34 and 49 have been rejected under 35 U.S.C. §103(a) as obvious over Rosenblum et al. in view of Chobanian et al.

The reasons for rejection are set forth in the Office Action of June 24, 2004 ("Office Action"), Final Office Action of January 27, 2005 ("Final Office Action") and Advisory Action of April 11, 2005 ("Advisory Action") summarized as follows:

In the Office Action, it is alleged that Rosenblum et al. teach the claimed ezetimibe compound as old and well known in combination with various pharmaceutical carriers and excipients in a dosage form. (See column 32, example 6). Office Action at page 4, lines 18-19. It is further alleged that this medicament is taught as useful for reducing cholesterol and treating arteriosclerosis (column 4, lines 50-66), at those levels herein envisioned. (See column 20, line 21). Office Action at page 4, line 20 to page 5, line 2.

In the Office Action, it is alleged that Chobanian et al. teach the claimed captopril cardiovascular agent as old and well known in combination

with various pharmaceutical carriers and excipients in a dosage form and that this medicament is taught as useful for reducing cholesterol and treating arteriosclerosis, at those levels herein envisioned. (See abstract). Office Action at page 5, lines 3-6.

In the Office Action, it is acknowledged that Claims 1, 3, 22-23, 33-34 and 49, and the primary references, differ as to: 1) the concomitant employment of these medicaments, and 2) the intended use for the compositions.

However, the Office Action states that it is generally considered prima facie obvious to combine two, or more, compounds each of which is taught by the prior art to be useful for the same purpose, in order to form a composition which is to be used for the very same purpose, the idea for combining them flowing logically from their having been used individually in the prior art. In the Office Action, it is alleged that the instant claims define nothing more than the concomitant use of conventional anti-arteriosclerosis agents and that the recited claims define prima facie obvious subject matter, citing In re Kerhoven, 626 F.2d 848, 205 USPQ 1069 (CCPA 1980). Office Action at page 5, lines 10-17.

The Office Action further states that Claim 49 specifically requires a pharmaceutical composition for various therapeutic uses and that Examiner-cited prior art employed the claimed compounds for various vascular therapeutic uses, not specifically reciting other uses for the formulation. Office Action at page 5, lines 18-20.

The Office Action directs Applicants' attention to In re Dillon, 16 USPQ2nd 1897 at 1900 (CAFC 1990). The court sitting en banc ruled that the recitation of a new utility for an old and well known composition does not render that composition new. Office Action at page 6, lines 1-3.

In the Final Office Action, Applicants' arguments were characterized as unpersuasive because Rosenblum et al. allegedly teach a combination of compound of formula (I) with another cholesterol reducing compound, a cholesterol biosynthesis inhibitor, for the treatment of atherosclerosis. It is

alleged that one would be motivated to combine captopril, which is taught as useful for reducing cholesterol and treating arteriosclerosis with another cholesterol lowering agent such as formula (I) taught by Rosenblum et al. to obtain a medicament which is more effective in treating arteriosclerosis. Final Office Action at page 2, lines 17-22.

In the Advisory Action, Applicants' arguments were characterized as unpersuasive because Rosenblum et al. allegedly teaches a method of treating atherosclerosis, comprising administering a combination of ezetimibe and a cholesterol biosynthesis inhibitor. Rosenblum et al. is alleged to further teach that the risk factors associated for atherosclerotic coronary heart disease, include hypertension, serum cholesterol etc. Thus, it is alleged that there is motivation to combine a compound of formula (I) with antihypertensive agent captopril with the expectation of obtaining a synergistic effect for the treatment of atherosclerosis because '966 teaches that hypertension and high serum cholesterol are risk factors for atherosclerosis. Advisory Action at page 2, lines 8-18.

Applicants argument that "the rejection of claims 43-45 is based upon improper hindsight reconstruction" was also characterized as not persuasive. Advisory Action at page 2, lines 17-18. It is alleged that Rosenblum et al. teach that the pharmaceutical compositions comprising compound of formula (I) can be prepared using conventional excipients and additives which include non-toxic compatible fillers, binders, disintegrants, buffers, preservatives, anti-oxidants, thickeners, emulsifiers etc. See column 21, lines 5-15. Advisory Action at page 2, lines 14-17. Thus, it is averred in the Advisory Action, there is motivation to add anti-oxidant, vitamin C, water soluble fiber etc. to the composition comprising a compound of formula (I), and an antihypertensive agent. Advisory Action at page 2, lines 17-18.

B. The Prior Art

Rosenblum et al. disclose the compound of Formula II (col. 32, Ex. 6). Rosenblum et al. disclose starch-based pharmaceutical compositions

including compounds of Formula I (col. 39, Ex. A and B). Rosenblum et al. teach that the active compounds therein can be combined with HMG CoA reductase inhibitors, such as simvastatin (col. 6, lines 37-49) for reducing cholesterol and the risk of atherosclerosis (claims).

Chobanian et al. disclose the use of captopril, an angiotension converting enzyme (ACE) inhibitor, for decreasing aortic atherosclerosis in hyperlipidemic rabbits, while increasing average serum cholesterol levels.

C. The Required Prima Facie Case of Obviousness Under 35 U.S.C. § 103 Has Not Been Established

When making a rejection under 35 U.S.C. § 103, the Examiner has the burden of establishing a prima facie case of obviousness. In re Fritch, 23 U.S.P.Q.2d 1780, 1783 (Fed. Cir. 1992). The Examiner can satisfy this burden only by showing an objective teaching in the prior art, or knowledge generally available to one of ordinary skill in the art, which would lead an individual to combine the relevant teachings of the references [and/or the knowledge] in the manner suggested by the Examiner. Id.; In re Fine, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988).

The mere fact that the prior art could be modified does not make the modification obvious unless the prior art suggests the desirability of the modification. In re Fritch, 23 U.S.P.Q.2d at 1784; In re Laskowski, 10 U.S.P.Q.2d 1397, 1398 (Fed. Cir. 1989); In re Gordon, 221 U.S.P.Q. 1125, 1127 (Fed. Cir. 1984). This desirability has not been shown in any of the references cited in any Office Action.

Specifically, the desirability of combining the two agents claimed, a cholesterol absorption inhibitor such as a compound of formula I shown in Rosenblum et al., in combination with an ACE-inhibitor such as captopril, as shown in Chobanian et al., is nowhere shown in the prior art.

Rosenblum et al. do not suggest or disclose a combination of a compound of formula (I) with a cardiovascular agent selected from the group consisting of channel blockers, adrenergic blockers, adrenergic stimulants,

angiotensin-converting enzyme (ACE) inhibitors, antihypertensive agents, angiotensin II receptor antagonists, anti-anginal agents, coronary vasodilators, diuretics and combinations thereof. Rosenblum et al. show the combination of a cholesterol absorption inhibitor with a cholesterol biosynthesis inhibitor, specifically a HMG CoA reductase inhibitor.

Chobanian et al. discloses that captopril, an ACE-inhibitor, may be useful for treating atherosclerosis. In fact, the treatment results shown in Chobanian et al. are equivocal. At page 329, left column, it is noted that serum cholesterol levels of captopril-treated rabbits were significantly greater than those in the control group. The effect of captopril on atherogenesis was restricted to the descending thoracic aorta of the treated rabbits (page 329, col. 1). Thus, the use of captopril alone for treating atherosclerosis in humans is not even strongly suggested in the Chobanian et al. study; further study of the drug is recommended at page 331, col. 1. Further, even if Chobanian et al. can be said to teach the use of captopril for treatment of atherosclerosis, which Applicants do not concede, it can also be said to teach away from the concept of use of two separate compounds (a compound of formula (I) and a separate cardiovascular agent as claimed) because captopril would serve both functions as an antihypertensive and a treatment for atherosclerosis.

Contrary to the assertions in the Office Action, the Final Office Action and the Advisory Action, the desirability of combining the compounds presently claimed, and a suggestion that the combination of the two categories of compounds would actually work together, is not shown in the references. Applicants respectfully submit that it is never obvious to combine two drugs into one dosage form. Drug-drug interactions are of great concern, and predictions of safety and efficacy cannot be made, *a priori*, based on knowledge of the individual compounds. Safety and efficacy studies of the combined compounds must always be undertaken. There is no way of knowing, prior to such testing, that the compounds, when administered in combination, will have the same profile as the compounds administered separately. Applicants respectfully submit that combining the Rosenblum et

al. and Chobanian et al. references renders the present claims at best "obvious to try", which is not the standard for patentability. "It is impermissible to use the claimed invention as an instruction manual or 'template' to piece together the teachings of the prior art so that the claimed invention is rendered obvious....'[o]ne cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention.'" In re Fritch, 23 U.S.P.Q.2d at 1784 (quoting In re Fine, 5 U.S.P.Q.2d at 1600). One skilled in the art would have no way of knowing, absent experimentation, whether the combination of compounds would work as asserted.

Therefore, one skilled in the art would not be motivated by the teachings of Rosenblum et al. and Chobanian et al., as combined in the Office Action, to provide a compound of formula (I) and a separate cardiovascular agent as presently claimed.

Applicants respectfully submit that Claims 1, 3, 22-23, 33-34 and 49 are not obvious in view of Rosenblum et al. and Chobanian et al. and request that the rejection of these claims under 35 U.S.C. §103(a) be reconsidered and withdrawn.

II. The Required Prima Facie Case of Obviousness Under 35 U.S.C. § 103 Over Rosenblum et al. and Chobanian et al., and further in view of Lelek et al., Myasnikov and Schaarmann et al. has Failed to be Established.

A. The Rejection

Claims 43-46 are rejected under 35 U.S.C. § 103 as being obvious over Rosenblum et al. in view of Chobanian et al. as set forth for claims 1, 3, 22-23, 33-34 and 49 above, further in view of Lelek et al., Myasnikov and Schaarmann et al.

The reasons for the rejection are set forth in the Office Action of June 24, 2004 ("Office Action"), the Final Office Action of January 27, 2005 ("Final Office Action") and Advisory Action of April 11, 2005 ("Advisory Action"), summarized as follows:

In the Office Action, it is alleged that Lelek et al. teach the claimed omega 3 fatty acids, (linolenic acid) as old and well known in combination with various pharmaceutical carriers and excipients in a dosage form. It is further alleged that this medicament is taught as useful for reducing cholesterol and treating arteriosclerosis at those levels herein envisioned. Office Action at page 6, lines 5-11.

In the Office Action, it is alleged that Myasnikov teaches the claimed vitamin C as old and well known in combination with various pharmaceutical carriers and excipients in a dosage form. It is also alleged that this medicament is taught as useful for reducing cholesterol and treating arteriosclerosis, at those levels herein envisioned. Office Action at page 6, lines 11-14.

In the Office Action, it is alleged that Schaarmann et al. teach the claimed soluble fiber as old and well known in combination with various pharmaceutical carriers and excipients in a dosage form. (See abstract). It is further alleged that this medicament is taught as useful for positively influencing the ration of HDL to LDL ratio, and thereby constructively reducing the cholesterol level and treating arteriosclerosis. Office Action at page 6, lines 14-18.

It is acknowledged in the Office Action that Claims 43-46, and the primary references, differ as to the concomitant employment of these medicaments. However, the Office Action states that it is generally considered prima facie obvious to combine two, or more, compounds each of which is taught by the prior art to be useful for the same purpose, in order to form a composition which is to be used for the very same purpose. The idea for combining them flows logically from their having been used individually in the prior art. As shown by the recited teachings, the instant claims define nothing more than the concomitant use of conventional anti-arteriosclerosis agents. It would follow that the recited claims define prima facie obvious subject matter. Cf. In re Kerhoven, 626 F.2d 848, 205 USPQ 1069 (CCPA 1980). Office Action at page 6, line 21 to page 7, line 6.

The Office Action further states that Claims 43-46 specifically require a pharmaceutical composition for various therapeutic uses. Examiner-cited prior art employed the claimed compounds for various vascular therapeutic uses, not specifically reciting other uses for the formulation. Office Action at page 7, lines 7-9.

The Office Action directs Applicants' attention to In re Dillon, 16 USPQ2nd 1897 at 1900 (CAFC 1990). The court sitting en banc ruled that the recitation of a new utility for an old and well-known composition does not render that composition new. Office Action at page 7, lines 10-12.

In the Advisory Action, Applicants argument that "the rejection of claims 43-45 is based upon improper hindsight reconstruction" was characterized as not persuasive. It was alleged that Rosenblum et al. teach that the pharmaceutical compositions comprising compound of formula (I) can be prepared using conventional excipients and additives which include non-toxic compatible fillers, binders, disintegrants, buffers, preservatives, anti-oxidants, thickeners, emulsifiers etc. See column 21, lines 5-15. It was concluded in the Advisory Action that there is motivation to add anti-oxidant, vitamin C, water soluble fiber etc. to the composition comprising a compound of formula (I), and an antihypertensive agent. Advisory Action at page 2, lines 17-18.

B. The Prior Art

Rosenblum et al. disclose the compound of Formula II (col. 32, Ex. 6). Rosenblum et al. disclose starch-based pharmaceutical compositions including compounds of Formula I (col. 39, Ex. A and B). Rosenblum et al. teach that the active compounds therein can be combined with HMG CoA reductase inhibitors, such as simvastatin (col. 6, lines 37-49) for reducing cholesterol and the risk of atherosclerosis (claims).

Chobanian et al. disclose the use of captopril, an angiotension converting enzyme (ACE) inhibitor, as decreasing aortic atherosclerosis in hyperlipidemic rabbits, while increasing average serum cholesterol levels.

Lelek et al. disclose the use of essential fatty acids in the treatment of atherosclerosis. There is no suggestion of the combination of an essential fatty acid in combination with captopril and a compound of formula I.

Schaarmann et al. disclose that ingestion of a diet high in soluble dietary fiber may enhance absorption of tocopherol (Vitamin E). There is no suggestion that a diet high in fiber may be combined with other treatments for atherosclerosis.

Myasnikov discloses the use of Vitamin C for treatment of atherosclerosis and reducing cholesterol levels.

C. The Required Prima Facie Case of Obviousness Under 35 U.S.C. § 103 Has Not Been Established

Claims 43-46 depend from claim 1 (drawn to a composition or therapeutic combination comprising a compound of formula (I) (such as ezetimibe) with a cardiovascular agent selected from the group consisting of channel blockers, adrenergic blockers, adrenergic stimulants, angiotensin-converting enzyme (ACE) inhibitors, antihypertensive agents, angiotensin II receptor antagonists, anti-anginal agents, coronary vasodilators, diuretics and combinations thereof).

Claim 43 recites the composition of claim 1, further comprising at least one Omega 3 fatty acid.

Claim 44 recites the composition of claim 1, further comprising at least one natural water soluble fiber.

Claim 45 recites the composition of claim 1, further comprising at least one antioxidant or vitamin.

As discussed above, one skilled in the art would not be motivated by the teachings of Rosenblum et al. and Chobanian et al., as combined in the Office Action, to provide a compound of formula (I) and a separate cardiovascular agent *selected from the group consisting of channel blockers, adrenergic blockers, adrenergic stimulants, angiotensin-converting enzyme (ACE) inhibitors, antihypertensive agents, angiotensin II receptor antagonists,*

anti-anginal agents, coronary vasodilators, diuretics and combinations thereof as presently claimed.

As noted above, Rosenblum et al. do not suggest using a compound of Formula I shown therein, a cholesterol absorption inhibitor, with any other category of compound besides a HMG CoA reductase inhibitor, a cholesterol biosynthesis inhibitor. Similarly, Chobanian et al. do not describe the use of combinations of compounds having different mechanisms of action, and actually teaches away from the concept of use of two separate compounds (a compound of formula (I) and a separate cardiovascular agent *selected from the group consisting of channel blockers, adrenergic blockers, adrenergic stimulants, angiotensin-converting enzyme (ACE) inhibitors, antihypertensive agents, angiotensin II receptor antagonists, anti-anginal agents, coronary vasodilators, diuretics and combinations thereof* as claimed) because captopril would serve both functions as an antihypertensive and treatment for atherosclerosis. As noted above, based on the data shown in Chobanian et al., the use of captopril alone for treating atherosclerosis in humans is not even strongly suggested, much less the use of captopril in combination with other compounds. Thus, Claims 43-46 are non-obvious and patentable in view of the cited references as combined in the rejection.

It is asserted in the Office Action that Lelek et al., Myasnikov and Schaarmann et al. teach that omega 3 fatty acids, vitamin C and soluble fibers, respectively, are useful for reducing cholesterol and treating atherosclerosis, rendering the combination of these compounds with the above combination obvious. Applicants disagree with these assertions.

First, Schaarmann et al. teach that high intake of dietary fiber does not deteriorate the absorption of tocopherol (vitamin E) in women. The relevance of this statement to treatment of atherosclerosis with the combination of compounds currently claimed is tenuous, at best. At page 693, last three sentences, Schaarmann et al. specifically state that only insignificant differences were measured in serum lipoprotein concentrations (between treated and control groups), and the total cholesterol concentration remained

unchanged. As with the Chobanian et al. reference, reliance on Schaarmann et al. in the obviousness rejection is unfounded, based on the data presented therein.

Lelek et al. and Myasnikov do not teach or suggest the use of the compounds described therein, in combination with any other compounds, nor the combination of compounds specifically claimed in Claim 1.

Following the reasoning presented in the Office Action, one skilled in the art would combine *every* compound that may have some minor activity in treating some aspect of hypocholesterolemia, which can encompass thousands of compounds. Yet no guidance is provided as to the selection of particular combinations of classes of compounds, i.e., cholesterol absorption inhibitor with *channel blockers, adrenergic blockers, adrenergic stimulants, angiotensin-converting enzyme (ACE) inhibitors, antihypertensive agents, angiotensin II receptor antagonists, anti-anginal agents, coronary vasodilators or diuretics,* or motivation for doing so. Applicants have selected particular classes of compounds, i.e., *channel blockers, adrenergic blockers, adrenergic stimulants, angiotensin-converting enzyme (ACE) inhibitors, antihypertensive agents, angiotensin II receptor antagonists, anti-anginal agents, coronary vasodilators or diuretics* to combine with sterol absorption inhibitor(s) not because a few species of these compounds may have some minor anti-cholesterol effect but because these compounds can have a complementary effect to treatment with the sterol absorption inhibitor.

As noted above in the discussion of the previous rejection, there is no way to know, absent testing, whether combinations of compounds having completely different mechanisms of action will actually work as expected. Applicants respectfully submit that the combination of three compounds as claimed in Claims 43-45 is not obvious in view of the references cited. There is simply no suggestion or evidence that the compounds will work together as asserted in the Office Action.

Claim 46 recites a pharmaceutical composition for the treatment or prevention of vascular conditions, obesity, diabetes or lowering a

concentration of a sterol in plasma of a mammal, comprising a therapeutically effective amount of the composition of Claim 1 and a pharmaceutically acceptable carrier.

As discussed above, and for all of the above reasons, one skilled in the art would not be motivated by the teachings of Rosenblum et al. and Chobanian et al., as combined in the Office Action, to provide a pharmaceutical composition comprising a compound of formula (I) and a separate cardiovascular agent *selected from the group consisting of channel blockers, adrenergic blockers, adrenergic stimulants, angiotensin-converting enzyme (ACE) inhibitors, antihypertensive agents, angiotensin II receptor antagonists, anti-anginal agents, coronary vasodilators, diuretics and combinations thereof* for the treatment or prevention of vascular conditions, obesity, diabetes or lowering a concentration of a sterol in plasma of a mammal.

Applicants respectfully assert that the rejection is based upon improper hindsight reconstruction and respectfully request that the rejection of claims 43-46 under 35 U.S.C. §103(a) be reconsidered and withdrawn.

Thus, Applicants respectfully request that the rejection of Claims 1, 3, 22, 23, 33, 34, 43-46 and 49 under 35 U.S.C. §103(a) be reconsidered and withdrawn.

Respectfully submitted,

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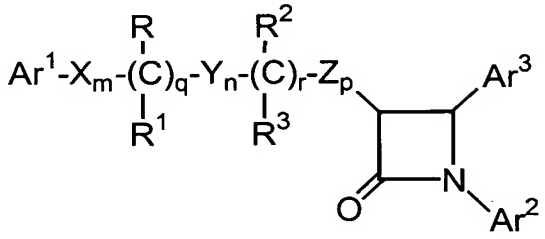
CLAIM APPENDIX

1. A composition comprising:

(a) at least one sterol absorption inhibitor represented by Formula (I):



(I)

or isomers thereof, or pharmaceutically acceptable salts or solvates of the compounds of Formula (I) or of the isomers thereof,

wherein:

Ar^1 and Ar^2 are independently selected from the group consisting of aryl and R^4-substituted aryl;

Ar^3 is aryl or R^5-substituted aryl;

X, Y and Z are independently selected from the group consisting of $-CH_2-$, -CH(lower alkyl)- and -C(dilower alkyl)-;

R and R^2 are independently selected from the group consisting of $-OR^6$, $-O(CO)R^6$, $-O(CO)OR^9$ and $-O(CO)NR^6R^7$;

R^1 and R^3 are independently selected from the group consisting of hydrogen, lower alkyl and aryl;

q is 0 or 1;

r is 0 or 1;

m, n and p are independently selected from 0, 1, 2, 3 or 4; provided that at least one of q and r is 1, and the sum of m, n, p, q and r is 1, 2, 3, 4, 5 or 6; and provided that when p is 0 and r is 1, the sum of m, q and n is 1, 2, 3, 4 or 5;

R^4 is 1-5 substituents independently selected from the group consisting of lower alkyl, $-OR^6$, $-O(CO)R^6$, $-O(CO)OR^9$, $-O(CH_2)_{1-5}OR^6$, $-O(CO)NR^6R^7$, $-NR^6R^7$, $-NR^6(CO)R^7$, $-NR^6(CO)OR^9$, $-NR^6(CO)NR^7R^8$, $-NR^6SO_2R^9$, $-COOR^6$, $-CONR^6R^7$, $-COR^6$, $-SO_2NR^6R^7$, $S(O)_{0-2}R^9$, $-O(CH_2)_{1-10}-COOR^6$, $-O(CH_2)_{1-10}CONR^6R^7$, -(lower alkylene)$COOR^6$, $-CH=CH-COOR^6$, $-CF_3$, -CN, $-NO_2$ and halogen;

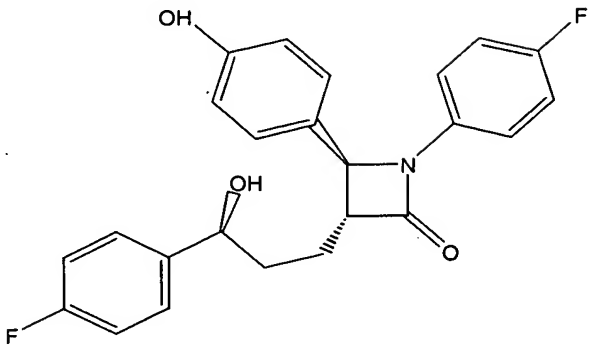
R^5 is 1-5 substituents independently selected from the group consisting of
$-OR^6$, $-O(CO)R^6$, $-O(CO)OR^9$, $-O(CH_2)_{1-5}OR^6$, $-O(CO)NR^6R^7$, $-NR^6R^7$, $-NR^6(CO)R^7$, $-NR^6(CO)OR^9$, $-NR^6(CO)NR^7R^8$, $-NR^6SO_2R^9$, $-COOR^6$, $-CONR^6R^7$, $-COR^6$, $-SO_2NR^6R^7$, $S(O)_{0-2}R^9$, $-O(CH_2)_{1-10}-COOR^6$, $-O(CH_2)_{1-10}CONR^6R^7$, -(lower alkylene)$COOR^6$ and $-CH=CH-COOR^6$;

R^6, R^7 and R^8 are independently selected from the group consisting of hydrogen, lower alkyl, aryl and aryl-substituted lower alkyl; and

R^9 is lower alkyl, aryl or aryl-substituted lower alkyl; and

(b) at least one cardiovascular agent for treating vascular conditions selected from the group consisting of channel blockers, adrenergic blockers, adrenergic stimulants, angiotensin-converting enzyme (ACE) inhibitors, antihypertensive agents, angiotensin II receptor antagonists, anti-anginal agents, coronary vasodilators, diuretics and combinations thereof.

3. The composition according to claim 1, wherein the sterol absorption inhibitor is represented by Formula (II) below:



(II)

or pharmaceutically acceptable salts or solvates thereof, or prodrugs of the compound of Formula (II) or of the salts or solvates thereof.

22. The composition according to claim 1, wherein the at least one cardiovascular agent is an antihypertensive agent.

23. The composition according to claim 22, wherein the antihypertensive agent is selected from the group consisting of althiazide, benzthiazide, captopril, carvedilol, chlorothiazide sodium, clonidine hydrochloride, cyclothiazide, delapril hydrochloride, dilevalol hydrochloride, doxazosin mesylate, fosinopril sodium, guanfacine hydrochloride, methyldopa, metoprolol succinate, moexipril hydrochloride, monatepil maleate, pelanserin hydrochloride, phenoxybenzamine hydrochloride, prazosin hydrochloride, primidolol, quinapril hydrochloride, quinaprilat, ramipril, terazosin hydrochloride, candesartan, candesartan cilexetil, telmisartan, amlodipine besylate, amlodipine maleate, bevantolol hydrochloride and combinations thereof.

33. The composition according to claim 1, wherein the at least one cardiovascular agent for treating vascular conditions is administered to a mammal in an amount ranging from about 50 to about 3000 milligrams of cardiovascular agent per day.

34. The composition according to claim 1, wherein the at least one sterol absorption inhibitor is administered to a mammal in an amount ranging from about 0.1 to about 1000 milligrams of sterol absorption inhibitor per day.

43. The composition according to claim 1, further comprising at least one Omega 3 fatty acid.

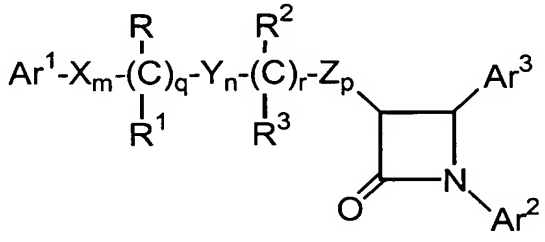
44. The composition according to claim 1, further comprising at least one natural water soluble fiber.

45. The composition according to claim 1, further comprising at least one antioxidant or vitamin.

46. A pharmaceutical composition for the treatment or prevention of vascular conditions, obesity, diabetes or lowering a concentration of a sterol in plasma of a mammal, comprising a therapeutically effective amount of the composition of claim 1 and a pharmaceutically acceptable carrier.

49. A therapeutic combination comprising:

(a) a first amount of at least one sterol absorption inhibitor represented by Formula (I):



(I)

or isomers thereof, or pharmaceutically acceptable salts or solvates of the compounds of Formula (I) or of the isomers thereof,

wherein:

Ar^1 and Ar^2 are independently selected from the group consisting of aryl and R^4-substituted aryl;

Ar^3 is aryl or R^5-substituted aryl;

X, Y and Z are independently selected from the group consisting of $-CH_2-$, -CH(lower alkyl)- and -C(dilower alkyl)-;

R and R^2 are independently selected from the group consisting of $-OR^6$, $-O(CO)R^6$, $-O(CO)OR^9$ and $-O(CO)NR^6R^7$;

R^1 and R^3 are independently selected from the group consisting of hydrogen, lower alkyl and aryl;

q is 0 or 1;

r is 0 or 1;

m, n and p are independently selected from 0, 1, 2, 3 or 4; provided that at least one of q and r is 1, and the sum of m, n, p, q and r is 1, 2, 3, 4, 5 or 6; and provided that when p is 0 and r is 1, the sum of m, q and n is 1, 2, 3, 4 or 5;

R^4 is 1-5 substituents independently selected from the group consisting of lower alkyl, $-OR^6$, $-O(CO)R^6$, $-O(CO)OR^9$, $-O(CH_2)_{1-5}OR^6$, $-O(CO)NR^6R^7$, $-NR^6R^7$, $-NR^6(CO)R^7$, $-NR^6(CO)OR^9$, $-NR^6(CO)NR^7R^8$, $-NR^6SO_2R^9$, $-COOR^6$, $-CONR^6R^7$, $-COR^6$, $-SO_2NR^6R^7$, $S(O)_{0-2}R^9$, $-O(CH_2)_{1-10}-COOR^6$, $-O(CH_2)_{1-10}CONR^6R^7$, -(lower alkylene)$COOR^6$, $-CH=CH-COOR^6$, $-CF_3$, -CN, $-NO_2$ and halogen;

R^5 is 1-5 substituents independently selected from the group consisting of
$-OR^6$, $-O(CO)R^6$, $-O(CO)OR^9$, $-O(CH_2)_{1-5}OR^6$, $-O(CO)NR^6R^7$, $-NR^6R^7$, $-NR^6(CO)R^7$, $-NR^6(CO)OR^9$, $-NR^6(CO)NR^7R^8$, $-NR^6SO_2R^9$, $-COOR^6$, $-CONR^6R^7$, $-COR^6$, $-SO_2NR^6R^7$, $S(O)_{0-2}R^9$, $-O(CH_2)_{1-10}-COOR^6$, $-O(CH_2)_{1-10}CONR^6R^7$, -(lower alkylene)$COOR^6$ and $-CH=CH-COOR^6$;

R^6, R^7 and R^8 are independently selected from the group consisting of hydrogen, lower alkyl, aryl and aryl-substituted lower alkyl; and

R^9 is lower alkyl, aryl or aryl-substituted lower alkyl; and

(b) a second amount of at least one cardiovascular agent selected from the group consisting of channel blockers, adrenergic blockers, adrenergic stimulants, angiotensin-converting enzyme (ACE) inhibitors, antihypertensive agents, angiotensin II receptor antagonists, anti-anginal agents, coronary vasodilators, diuretics and combinations thereof

wherein the first amount and the second amount together comprise a therapeutically effective amount for the treatment or prevention of a vascular condition, obesity, diabetes or lowering a concentration of a sterol in plasma of a mammal.

EVIDENCE APPENDIX

None.

RELATED PROCEEDINGS APPENDIX

None.